"conductive oligomer" component of the present invention is not disclosed by Marble, *et al.* As defined in the specification at page 16, line 14 through page 17, line 6:

> By "conductive oligomer" herein is meant a substantially conducting oligomer, preferably linear, some embodiments of which are referred to in the literature as "molecular wires". By "substantially conducting" herein is meant that the rate of electron transfer through the conductive oligomer is faster than the rate of electron transfer through single stranded nucleic acid, such that the conductive oligomer is not the rate limiting step in the detection of hybridization, although as noted below, systems which use spacers that are the rate limiting step are also acceptable. Stated differently, the resistance of the conductive oligomer is less than that of the nucleic acid. Preferably, the rate of electron transfer through the conductive oligomer is faster than the rate of electron transfer through double stranded nucleic acid, i.e. through the stacked π-orbitals of the double helix. Generally, the conductive oligomer has substantially overlapping π-orbitals, i.e. conjugated π-orbitals, as between the monomeric units of the conductive oligomer, although the conductive oligomer may also contain one or more sigma (σ) bonds. Additionally, a conductive oligomer may be defined functionally by its ability to inject or receive electrons into or from an attached nucleic acid. Furthermore, the conductive oligomer is more conductive than the insulators as defined herein.

Marble *et al.*, teach a method of preparing immoblilized DNA in which it is convenient to use templates in which the DNA is covalently linked to controlled pore glass (CPG) via a 3'-O-succinyl-ester. The covalently linked templates are activated by hybridizing the complementary T7 promoter, top-strand directly to the covalently linked RNA coding bottom strand. (CPG; see column 13, line 63 to column 14, line 11).

An anticipation rejection requires that a single reference expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)). Additionally, the reference must enable and describe the claimed invention "sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." 31 USPQ2d at 1673. To be enabling, the reference must teach the skilled artisan how to make and use the full scope of the claimed invention without undue experimentation. *See Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997).

As can be seen from the above discussion, although Marble *et al.*, disclose DNA covalently linked to CPG, Marble *et al.*, does not teach a composition comprising a conductive oligomer covalently attached to a CPG nucleoside. Therefore, Marble, *et al.*, do no teach or suggest each and every element of the claimed invention. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection of Claim 57 under 35 U.S.C. § 102(e) as being anticipated by Marble, *et al.*

Claims 66 and 67 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Sargent *et al.* (P/N 5,601,982). Applicants submit that Sargent *et al.*, do not disclose the same composition as disclosed in Claims 66 and 67. Claims 66 and 67 claim a composition comprising a deoxynucleotide triphosphate, a metallocene and a conductive oligomer. The "conductive oligomer" component of Claims 66 and 67 is not disclosed by Sargent, *et al.*

The definition of a conductive oligomer is provided above.

Sargent *et al.* teach a method for determining the sequence of nucleic acids using scanning tunneling microscopy. In order to sequence nucleic acids using scanning tunneling microscopy, a nucleic acid molecule is labeled with a base specific label that allows the labeled base to be distinguished from adjacent base. Both the labels and methods of synthesizing chemically or enzymatically modified nucleic acids are those generally known to those in the art. Thus, Sargent *et al.*, use methods known to those of skill in the art to provide nucleic acids labeled with suitable labels that can be used for sequencing nucleic acids using scanning tunneling microscopy. See column 2, lines 4-41. Sargent *et al.* do not teach or suggest the use of conductive oligomers.

As amended, claim 66 is directed to a composition comprising a deoxynucleotide triphosphate comprising a covalently attached metallocene and a conductive oligomer. Sargent *et al.* do not teach nucleic acid molecules modified with conductive oligomers. Thus, Sargent *et al.*, do not teach all limitations of the invention as presently claimed. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claim 66 and claim 67 dependent therefrom.

Rejections Under 35 U.S.C. § 103(a):

Claims 62 to 65 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sargent *et al.* (P/N 5,601,982).

Sargent *et al.*, is discussed above.

As amended, Claim 62 is directed to a composition comprising a phosphoramidite nucleoside covalently attached to a metallocene and a conductive oligomer.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

Independent Claim 62 and dependent Claims 63-65 disclose a composition comprising a phosphoramidite nucleoside covalently attached to a metallocene and a conductive oligomer. As outlined above, Sargent *et al.*, do not disclose the use of conductive oligomers. Accordingly, Applicants submit there is no suggestion in Sargent to make the composition disclosed in Claim 62.

The Examiner states that Claims 62-65 are unpatentable over Sargent *et al.* Applicants disagree because the teachings of Sargent do not teach or suggest each and every limitation of Claims 62-65.

In view of the above, Applicants submit that claim 62, and claims 63 to 65 dependent therefrom, are unobvious over Sargent *et al.* Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 62 to 65.

Claims 58, 61 and 62 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Heller *et al.* (P/N 5,849,486). Applicants respectfully submit that Heller et al. do not teach or suggest a passivation agent layer comprising conductive oligomers, as required in the claimed invention.

Heller *et al.* reports a method for concentrating and reacting analytes at specific microlocations (column 11, lines 9-11). This is accomplished by using electrophoretic forces to transport charged compounds (column 10, lines 25-33). This method uses electrodes covered by a permeation layer (column 12, lines 26-27). The permeation layer precludes DNA from contacting the electrode directly (column 10, lines 6-9). The purpose of the permeation layer is to allow passage of ions sufficient for electrophoresis but to prevent the destruction of the nucleic acids attached to the "outer" surface of the permeation layer. The permeation layer can be formed using materials such as metal oxides, ceramics, carbon polymers and glass (column 12, line 27-31 and column 17, line 64 to column 18, line 6).

In contrast, claim 58 is directed to an electrode comprising a monolayer comprising a passivation agent layer comprising conductive oligomers, and at least one nucleic acid covalently attached to the electrode with a spacer.

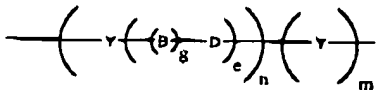
The Office Action indicates that the permeation layer of Heller et al. is reasonably interpreted as the recited passivation layer. Further, the Office Action points to the attachment of nucleic acid to the permeation layer via poly-l-lysine, which poly-l-lysine "is reasonably interpreted as an insulator." Applicants respectfully disagree.

As discussed above, a *prima facie* case of obviousness requires 3 elements: 1) motivation to combine references; 2) a reasonable expectation of success; and 3) that every element of the claims be found in the prior art.

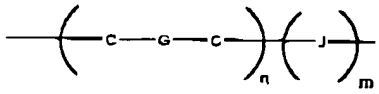
As a preliminary matter, Heller *et al.* does not teach or suggest the use of conductive oligomers. Applicants emphasize that the purpose of the permeation layer of Heller and the present passivation layer is completely different: Heller requires the passage of ions, while the present invention requires a lack of passage of ions (see specification at page 45, lines 3-13. Thus, not only is there no motivation in Heller, Heller actually teaches away from the present invention. As the Examiner is aware, a reference which leads one of ordinary skill away from the claimed invention cannot serve as a proper §103 reference.

In addition, Applicants respectfully submit that Heller *et al.* do not teach or suggest a passivation agent layer comprising conductive oligomers, as required in the claimed invention. Specifically, Heller *et al.* does not teach a passivation layer comprising

conductive oligomers (see specification at page 46, lines 21-24). When the passivation agent comprises a conductive oligomer, the conductive oligomer can have one of the structures depicted below:



wherein
Y is an aromatic group;
n is an integer from 1 to 50;
g is either 1 or zero;
e is an integer from zero to 10;and
m is zero or 1;
wherein when g is 1, B-D is a conjugated bond; and
wherein when g is zero, e is 1 and D is preferably carbonyl, or a heteroatom moiety, wherein the heteroatom is selected from oxygen, sulfur, nitrogen, silicon or phosphorus.
or



wherein
n is an integer from 1 to 50;
m is 0 or 1;
C is carbon;
J is carbonyl or a heteroatom moeity, wherein the heteroatom is selected from the group consisting of oxygen, nitrogen, silicon, phosphorus, sulfur; and
G is a bond selected from alkane, alkene or acetylene.

See specification at page 3, line 13 through page 4, line 11.

Moreover, Heller *et al.*, do not teach insulators as defined in the specification at page 47, lines 19-22:

> Suitable insulators are known in the art, and include, but are not limited to, $-(CH_2)_n-$, $-(CRH)_n-$, and $-(CR_2)_n-$, ethylene glycol or derivatives using other heteroatoms in place of oxygen, i.e. nitrogen or sulfur (sulfur derivatives are not preferred when the electrode is gold).

Finally, the passivation agents of the present invention are generally attached to the electrode in the same manner as the conductive oligomer, and may use the same "A" linker as defined above. See specification at page 47, lines 23-25.

Even assuming, *arguendo*, that motivation exists, there is no reasonable expectation of success. The present invention relies, in part, on the "shielding" of the

electrode to charge carriers in the solution. Adding a "permeation layer," which by definition is "permeable" would "short circuit" the present invention. Accordingly, a *prima facie* case by obviousness has not been established.

In view of the lack of teaching or suggestion of all claimed elements and a lack of motivation for one skilled in the art to modify the disclosure of Heller et al., Applicants submit that claim 58, and claims 60 and 61 dependent therefrom, are unobvious over Heller et al. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 58, 60 and 61.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current Amendment". The attached page is captioned **"Version with markings to show changes made."**

The applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited. If after review, the Examiner feels that there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

Dated: 11/20/01

Respectfully submitted,

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Serial No.: 08/873,978
Filing Date: June 12, 1997

"Version with markings to show changes made."

In the specification:
Paragraph beginning at line 1 of page 1 has been amended as follows:

ELECTRODES LINKED VIA CONDUCTIVE OLIGOMERS TO NUCLEIC ACIDS AND ELECTRON TRANSFER MOIETIES

In the Claims:
Claim 62 has been amended as follows:

62. (Amended) A composition comprising a phosphoramidite nucleoside covalently attached to a metallocene and a conductive oligomer.

66. (Amended) A composition comprising a deoxynucleotide triphosphate comprising a covalently attached metallocene and a conductive oligomer.

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Appendix of Pending and Allowed Claims

47. (Amended) A conductive oligomer comprising an ethyl-pyridine protected sulfur atom. (Allowed)

48. (Amended) A conductive oligomer comprising a trimethylsilylethyl protected sulfur atom. (Allowed)

57. A composition comprising a conductive oligomer covalently attached to a CPG-nucleoside.

58. An electrode comprising:
a) a monolayer comprising a passivation agent layer comprising conductive oligomers; and
b) at least one nucleic acid covalently attached to said electrode with a spacer.

59. (Amended) A composition according to claim 58 wherein said spacer is a conductive oligomer.

60. (Amended) A composition according to claim 58 wherein said spacer is an insulator.

61. (Amended) A composition according to claim 58 wherein said passivation agent layer further comprises insulators.

62. (Amended) A composition comprising a phosphoramidite nucleoside covalently attached to a metallocene and a conductive oligomer.

63. A composition according to claim 62 wherein said nucleoside comprises a ribose and said metallocene is covalently attached to the 2' position of said ribose.

64. A composition according to claim 62 wherein said metallocene is covalently attached to the base of said nucleoside.

65. A composition according to claim 62 wherein said metallocene is ferrocene.

66. (Amended) A composition comprising a deoxynucleotide triphosphate comprising a covalently attached metallocene and a conductive oligomer .

67. A composition according to claim 66 wherein said metallocene is ferrocene.